

Tuberculosis Associations throughout California have been working for several years should approach fruition at this time. In many counties and localities diagnostic surveys are under way or in prospect. Standard portable x-ray outfits are being used in some cases, fluoroscopes in others. In Los Angeles city and county a fluorographic unit similar to those used by the Army, but mounted on a large truck so it can be easily transported from place to place, has just been received. Other similar units are on order for other Associations, and delivery is expected within a matter of months. These are capable of surveying several hundred persons per day.

The policy of the Tuberculosis Associations is to make such surveys as demonstrations. They hope to convince the various groups concerned, both industry and labor, that it is to their advantage to take over the work ultimately and conduct it at their own expense. The Garment Workers' Union of New York City made a survey of its members several years ago. Many organizations in California are giving a rather complete physical examination to all applicants for employment. Frequently an x-ray film of the chest is included, and not a few cases of pulmonary disease are being uncovered.

The United States Public Health Service has eight 35 mm. fluorographic units in various portions of the country doing similar work, particularly among groups whose living conditions are substandard. They plan to add ten more units shortly.

As a result of all these and other surveys, numbers of unsuspected cases of active tuberculosis have been brought to light, and we can confidently expect more as the work progresses. In the aggregate the number will be very large.

SPECIAL PROBLEMS

Two important questions now present themselves:

The provision of sanatorium accommodations for the patients requiring treatment will be a very serious problem. An extremely high proportion of the smaller private sanatoria and rest homes are having to close their doors because of inability to secure help. Many counties, particularly those in which large war industries have developed, are going to find their need for beds much greater than their capacity. The nonresident character of a large portion of their population will add to their difficulties.

On the diagnostic side there will be much work to be done. All those with positive or suspicious x-ray findings on these miniature films, or on fluoroscopy will require films of standard size and a careful clinical examination to determine whether definite evidence of disease is present, and, if so, whether it is old and needs only periodic observation, or is active and, therefore, requires treatment.

These individuals are going to come for examination and advice to all of us, general practitioners, surgeons, internists and members of all

the other specialties. And here lies one of our great opportunities. Already some of them have asked for bread and been given a stone. The diagnosis or suspicion voiced at the induction center or the employment office has been ridiculed or brushed aside as without foundation, oftentimes to the serious detriment of the patient.

It is true that it is not easy to establish the status of many of these cases. The determination of the instability or obsolescence of their lesions may call for a most painstaking and time-consuming study. Such a study, however, is one to which the patient is entitled and one which we, as a profession, are obligated to supply, unless we believe he is a legitimate subject for care by the official health agencies. And having determined that the lesion is unstable or active, we must see that the patient is offered at the earliest possible moment the full benefit of all the great advances that modern medical science has developed. "A stitch in time, saves nine" is more true than ever of the treatment of tuberculosis. To see that these young people are given the opportunity for early and accurate diagnosis, and adequate scientific treatment in the stage when the disease is curable and rehabilitation to full membership in society possible—herein lies our opportunity and responsibility as a profession.

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EXTREME INSULIN RESISTANCE IN DIABETES*

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REMARKABLY few cases of extreme insulin resistance have been reported in the literature. Martin, Martin, Lyster and Strouse,¹ in a critical review of the literature, reported 26 cases which fulfilled their criteria of insulin resistance, i.e., "those cases in which, after forty-eight hours of observation, 200 or more units of insulin were required without effecting an appreciable lowering of the blood sugar." These cases were divided into 5 etiological groups: 1) Disturbance of endocrine glands—5 cases; 2) Infection—5 cases; 3) Hepatic disorders—5 cases; 4) Diseases of the skin and allergy—8 cases, and 5) Unexplained—2 cases.

To the literature we add the following case.

REPORT OF CASE

A 67-year-old Jewish man entered the hospital with symptoms of weight loss and inability to rid his urine of sugar. Four and one-half years prior to this entry, in a routine preoperative examination, sugar had been detected in his urine. He was controlled on 15 units of regular insulin three times a day. At the end of a year

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his blood sugar levels were low enough to allow insulin therapy to be discontinued.

Seven months prior to admission, he noted polydipsia and polyuria, but did not seek medical care until five months before entering the hospital. At that time, 15 units of protamine zinc insulin a day kept his urine sugar-free. Two or three months before hospitalization he began losing weight, and one month before entry it became evident that 15 units of protamine zinc insulin were insufficient to keep his urine free of sugar. At the time of admission, the dosage had been increased to 35 units a day, but glycosuria persisted.

Past History:—Some twenty-five years ago, he had had asthma. At that time it was learned that he was allergic to a colorless dye used on the furs with which he worked. When he avoided contact with the dye, his symptoms disappeared. Yet, throughout the ensuing years he often became "choked up" for short periods of time. During the ten years prior to his initial hospitalization, he had recurrent anginal attacks, which readily responded to nitroglycerine. One year ago he had a dermatitis of the extremities, which responded slowly to nonspecific therapy, and which may have been allergic in origin.

Family History:—There was no history of allergy or diabetes in this man's family.

Systemic Review:—All systems were essentially normal, except for the history of anginal attacks.

Physical Examination:—When first seen, the patient was ambulatory and entirely without complaints. He was a well-developed, well nourished man. His weight was 60.2 Kgm. The lungs were clear; the heart was very slightly enlarged; the sounds were regular in rhythm and force, and of a fair quality. The blood pressure was 124/78. An electrocardiogram revealed an abnormal record suggestive of coronary artery disease. The urinalysis revealed 4 plus sugar, but no acetone or diacetic acid. The blood sugar level was 426 mg. per cent.

Hospital Course:—At first the patient's hospital course was uneventful. He was started on a diet of 1,680 calories (C. 160, P. 80, F. 80). Three doses of crystalline insulin, a total of 65 units, reduced his fasting blood sugar level to 196 mg. per cent before breakfast on the second hospital day (Chart 1). On the ensuing days he received 130, 80, 105, and 220 units of crystalline insulin without a noticeable alteration in his blood sugar level.

On the sixth day, the dosage was increased to 565 units; the fasting blood sugar was 396 mg. per cent on the morning of the seventh day. On the seventh day he received 550 units of regular insulin subcutaneously in addition to 2 intravenous doses of 50 units each. On the

eight day, he received 700 units of regular insulin subcutaneously, 50 units of regular insulin intravenously, and later, 100 units more of regular insulin intravenously, a total of 850 units. Following the last dose of regular insulin given intravenously, he developed a generalized urticaria. Two 0.3 c.c. injections of 1/1000 adrenalin brought prompt relief, but precipitated a mild anginal attack which in turn was relieved by nitroglycerine.

On the morning of the ninth day his fasting blood sugar level was 274 mg. per cent, and on that day he received 640 units of crystalline and 240 units of protamine zinc insulin. He continued to have hives severely enough to require adrenalin for relief. On that same day, his carbon dioxide combining power was 52.1 vol. per cent. On the tenth day, 720 units of crystalline and 480 units of protamine insulin were given. He again had urticaria. On the morning of the eleventh day, his fasting blood sugar level was 268 mg. per cent; once again he received 720 units of crystalline insulin and 480 units of protamine zinc insulin. The hives recurred, but were much less severe.

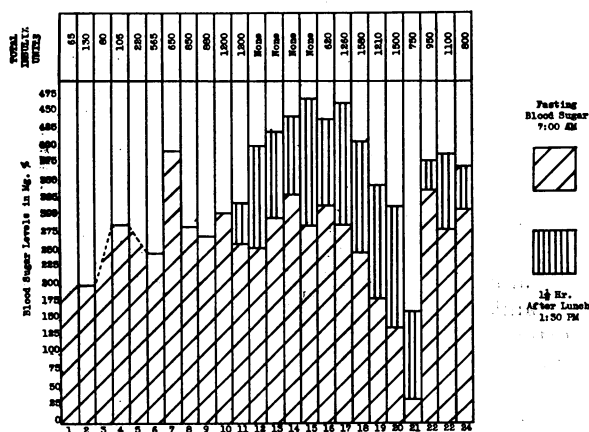


Chart 2.—Graphic relationship of blood sugar levels and insulin dosage.

The fasting blood sugar on the twelfth day was 263 mg. per cent. No insulin was administered, and during his thirteenth, fourteenth and fifteenth hospital days he received no insulin. His blood sugar levels increased steadily (Chart 2). Due to the fact that his weight had dropped to 58.7 Kgm., his diet was increased on the fourteenth day to 1930 calories (C. 180, P. 100, F. 90). During this time, the patient had no subjective complaints. He was up and around, and often walked about the hospital grounds.

On the morning of the sixteenth day, his fasting blood sugar level was 313 mg. per cent. He was again given crystalline insulin: 620 units in 16 doses. Later that day, acetone was first detected in his urine. His acid phosphatase was 0.3 units, and his alkaline phosphatase was 2.8 units. On the seventeenth day, the fasting blood sugar level was 286 mg. per cent. Eleven doses of crystalline insulin brought the total amount received to 1,260 units. He still showed traces of acetone. The fasting blood sugar on the eighteenth day was 253 mg. per cent. Nine doses of crystalline insulin, a total of 1,580 units, were given. By the end of the day all traces of acetone had disappeared.

On the nineteenth day, the fasting blood sugar was 186 mg. per cent; 250 units of U500 special insulin (later learned to be regular insulin) and 960 units of crystalline insulin, a total of 1,210 units, were given. Once again he complained of hives. No acetone was found in his urine. The fasting blood sugar on the morning of the

HOSP. DAY	INSULIN				BLOOD SUGAR IN MG. %				COMMENT
	Regular	Cryst.	Protamine	TOTAL	7:00 AM	1:30 PM	5:45 PM	10:00 PM	
1	45			45	426				Feeling well-ambulatory
2	130			130	196				
3	80			80					
4	105			105	294				
5	220			220	250		336		
6	565			565	396				
7	550+160*			550	396				I.V. Regular Insulin
8	700+160*			700	396				Hurticaria
9	640	240		880	274				Hives, Cereb. Comb. p. 62.1
10	720	480		1200	310				Hives.
11	720	480		1200	268	330			Hives.
12					263	400	308	370	Hives. No Insulin given.
13					301	421	374	378	Feeling perfectly well.
14					331	449	358	377	
15					292	470	406	471	
16	620			620	313	444	381	428	Insulin again. Acetone.
17	1260			1260	266	471	412	374	Acetone in urine.
18	1580			1580	253	412			Acetone.
19	250†	960		1210	186	333			Hives.
20	1800†			1800	140	318			Pain in right arm. Hives.
21	750†			750	33	149	72		Pain in rt. arm & l. leg.
22	950†			950	333	351			Abd. Pain in l. wrist.
23	300†	800		1100	286	382			Left 2 legs T. 101 P.
24		800		800	170	370			Cardiac death.
* Intermediate Insulin					† 100% R. Insulin				

* Intravenous insulin.

† U500 Regular Insulin.

Chart 1.—Insulin, dosage, blood sugar level, and clinical status.

twentieth day was 140 mg. per cent. He received 1,500 units of U500 (regular) insulin. He suffered from hives, intermittently, all day. He complained of pain along the distribution of the ulnar nerve in the right hand. On the twenty-first day, his fasting blood sugar level was 33 mg. per cent; 750 units of U500 (regular) insulin were administered. The patient felt well until about 1:30 P.M., at which time he was seized with an excruciating pain in his left leg and right arm, and was compelled to go to bed. His temperature rose to 100.4 F.

On the twenty-second day the fasting blood sugar level was 333 mg. per cent. He was given 950 units of U500 (regular) insulin. Pain was still present in his leg and right arm, but less severe. He had additional pain with swelling in his left wrist. The blood sedimentation rate was 24 mm. in 60 minutes. His fasting blood sugar level was 286 mg. per cent on the morning of the twenty-third day; 300 units of U500 (regular) and 800 units of crystalline insulin were given. Although pain in the extremities had entirely disappeared, he found it impossible to maintain a comfortable position. Later in the day he complained of "constricting" pain across the anterior aspect of his chest, which was only partially relieved by nitroglycerine. His blood pressure fell to 108/68, whereas his temperature remained elevated at about 101 F.

On the twenty-fourth day his fasting blood sugar level was 320 mg. per cent. Acetone was again manifest. Eight hundred units of crystalline insulin were administered. After breakfast the chest pain became marked. His blood pressure was 100/68. In the early evening he became very distressed, had difficulty getting his breath, and became ashen in color. An electrocardiogram revealed additional deviation from the normal. He was placed in an oxygen tent at 9 P.M., and died of cardiac failure at 12 midnight.

COMMENT

Unfortunately, permission to perform an autopsy was not obtainable. We are as yet unable to reach a definite conclusion as to the cause of our patient's resistance to insulin. This case is presented in the hope that it may contribute to an eventual solution of the problem of insulin resistance.

Following is the etiological classification of Martin, Martin, Lyster and Strouse¹:

1. Disturbance of Endocrine Glands:

Clinically, there was no apparent hormonal dysfunction. The basal metabolic rate was normal.

2. Infection:

No evidence of infection was discovered. At first the blood sedimentation rate was not increased; the white blood cell count was not elevated, and the patient remained afebrile until just prior to death.

3. Hepatic Disorders:

No signs or symptoms of liver disorder were present. The alkaline phosphatase test was normal.

4. Diseases of the Skin and Allergy:

The manifestations of allergy will be discussed.

5. Unexplained: Was the heart disease a factor?

As far as could be determined, there were but two pathologic conditions present, aside from the Diabetes Mellitus: a) Allergy, and b) Angina. Though the latter is probably of little significance,

it is interesting to note that Duncan² lists cardiovascular disease, i.e., 1) "Atheromatous changes in arteries," and 2) "The more explicable myocardial insufficiency with edema as conditions which may detract from the effectiveness of insulin." Also worthy of note is the account of a case of insulin resistance and sensitivity which was accompanied by frequent anginal attacks.³

DISCUSSION

Allergy was a striking feature in the case we have presented. One cannot say that the allergy and resistance followed a clear "cause and effect" pattern, but certainly the evidence is suggestive. As previously stated, the patient gave a history of asthma which occurred twenty-five years prior to hospitalization. There had been no subsequent, clinically recognized manifestations of allergy until during the period of hospitalization. On admission there was a mild eosinophilia, but no symptoms of allergy were evidenced until the eighth day. Insulin resistance, had been apparent for three days; however, it undoubtedly had been present in a milder form for some weeks previous to this.

In regard to the etiology of the sensitivity to insulin, three features are to be considered: 1) the dose, 2) the route of administration, and 3) the type of insulin.

1) *The Dose*:—The day of, and the one prior to the appearance of hives, the patient received 650 and 850 units of insulin, respectively. As this was given in U100 form, the volume injected was considerable. However, during the following week when even greater doses of insulin were administered, hives did not always appear. In order to eliminate a possible antigenic factor which might have been present only when the volume of insulin was great, U500 insulin was obtained from the Eli Lilly laboratories. It became apparent that the patient was equally sensitive to this concentrated form, as generalized urticaria followed shortly upon its injection.

2) *The Route of Administration*:—Regular insulin was given intravenously to determine the rôle of absorption. Large doses elicited no corresponding fall in the blood sugar level; thus it was demonstrated to our satisfaction that faulty absorption was no contributing factor. Urticaria was first noted after the patient had been maintained on intravenous therapy for forty-eight hours. And yet, the administration of insulin by this route did not provoke a sensitivity to insulin, *per se*, as evidenced by the absence of allergic response on certain subsequent days.

3) *The Type of Insulin*:—Three types of insulin were used. Regular, crystalline, and protamine zinc. Urticaria followed the administration of regular insulin given intravenously. Later, when U500 regular insulin was employed, hives appeared within one-half hour after its subcutaneous injection. Although the use of U500 insulin was continued over a period of five days, no urticaria appeared after the first forty-eight hours. However, by this time the patient's cardiac condition presented a serious complication.

Protamine zinc insulin was never tried alone, but when administered with the crystalline form, hives appeared each day. Of the three types employed, crystalline insulin was the only one to which there was no allergic response, but this fact was not clearly ascertained until late in the course of the patient's illness.*

Several days prior to death the patient suffered a coronary attack. It is difficult to say just when this occurred, but there were clinical signs present, such as fall in blood pressure and muffled heart-sounds, as early as the twenty-first hospital day. Under a régime of continual massive therapy, the fasting blood sugar level on the twenty-first day had fallen to 33 mg. per cent. Although the patient had none of the usual symptoms of an insulin reaction, it is possible that this hypoglycemic state precipitated a heart attack. Pain in the extremities seemed to be of a neuritic type and not associated with cardiac embarrassment.

On the twenty-fourth day, cardiovascular collapse terminated in death.

SUMMARY

A case of diabetes is presented in a patient, aged 67, who had been controlled for years on moderate doses of insulin. Within a period of a few months a resistance to insulin developed. There were no pathologic processes evident other than allergy and angina. The results obtained with massive doses of insulin are reported. Following an unexplained fall in the blood sugar, the patient died of acute heart failure.

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THE CLINICAL DIAGNOSIS OF CEREBELLAR INJURIES*

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ALTHOUGH the cerebellum occupies a sheltered position in the skull it is often affected, in some degree, by a blow on the head. Unless it be severely damaged, the complaints and signs may be overlooked until, during convalescence, the patient notices subtle disturbances although objective signs may not be apparent. The early signs of cerebellar injury are definite and not difficult to elicit. With this information, any later symptoms can be better understood, allowing a more exact prognosis.

PHYSIOLOGY

The cerebellum is concerned in the coordinating and regulating of muscle action. It keeps the muscles ready to respond to voluntary stimuli or to patterns of movement for which paths have been formed in the cerebral hemispheres. In learning to walk we first had to decide which foot to move forward, how far to advance it, and when to change the body weight from one foot to the other. Neural paths for this are developed in the cerebral hemispheres and each system of paths is called an engram, which represents the educated portion of an automatic act. But we never have had to decide, in making a movement, which antagonistic muscles to relax, which to hold a little taut or how to support the shoulders while using the hand. Such functions depend on the cerebellum. The mechanisms of balance and orientation in space depend largely on the cerebellum, which coordinates impulses from almost all of the special senses and from some of the general senses, and then sends its impulses to all of the muscles.

ANATOMY

The cerebellum, broadly, consists of right and left hemispheres with the vermis between them. The cortex, of tremendous extent, is folded like the leaves of a book, and all the emerging fibers converge to the few nuclei of nerve cells deep in the white matter. Fibers from here connect by the three cerebellar peduncles with the cerebrum, pons and medulla.

The cerebellar cortex contains at least eight wide-spread systems of diffuse communion among its several types of cell. This results in millions of alternate paths from one part of the cerebellum to another. For this reason, large areas of cerebellum may be destroyed or removed and the remaining tissue can, by reeducation, carry on almost the same functions as the whole organ.

In the cerebrum, the hemisphere of one side controls the opposite side of the body, but in the

*The concentrated insulin used was very kindly supplied by the Eli Lilly Laboratories. Due to unavoidable circumstances, it was several days before we knew that the material was "regular" insulin instead of a solution of zinc insulin crystals.

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